AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A non-human transgenic animal capable of producing heterologous T-cell receptors, comprising:

inactivated endogenous T-cell receptor loci; and

transgenes contained within its genome composed of unrearranged human T-cell receptor alpha and beta loci, wherein expression of the transgenes is controlled by human T-cell receptor loci regulatory sequences and wherein said animal is capable of productive rearrangement of the human T-cell receptor alpha and beta loci.

2. (Original) The non-human transgenic animal of claim 1, wherein said inactivated endogenous T-cell receptor loci are α and β chain T-cell receptor loci.

3. (Cancelled)

4. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said human T-cell receptor loci are composed, in operable linkage, of a plurality of human T-cell receptor V genes, and D and /or J and C genes.

5. (Currently Amended) The non-human transgenic animal as in one of claims 1-2, wherein said animal is capable of productive VDJC rearrangement and is capable of expressing heterologous T-cell receptors.

6. (Previously presented) The non-human transgenic animal as in one of claims 1- 2, wherein said transgenes undergo productive VDJC rearrangement in lymphocytes of said non-human transgenic animal and wherein T-cells express detectable amounts of transgenic TCR in response to antigenic stimulation.

7. (Previously presented) The non-human transgenic animal as in one of claims 1- 2 wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to an antigen and wherein the T-cell receptors comprise a human T-cell receptor.

8. (Cancelled)

9-29 (Cancelled)

30. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is any animal which can be manipulated transgenically.

31. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is a mouse.

32 – 37 (Cancelled)

38. (Currently Amended) A method of producing a non-human transgenic animal capable of productive rearrangement of the human T-cell receptor α and β loci and of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell;

inserting transgenes containing active, unrearranged α and β chain human T-cell receptor loci in said embryo or embryonic stem cell, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene wherein the animal is capable of producing T-cells that express human T-cell receptors; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

39. (Original) The method of claim 38 wherein said endogenous T-cell receptor loci are α and β chain T-cell receptor loci.

40. (Cancelled)

41. (Currently amended) A method of producing a non-human transgenic animal capable of productive rearrangement of the human T-cell receptor α and β loci and of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell, wherein said loci are T-cell receptor α or T-cell receptor ß loci;

producing a transgenic animal from said embryo or embryonic stem cell which contains inactivated loci wherein the animal is incapable of expressing said endogenous loci;

crossing a produced transgenic animal having inactivated endogenous T-cell receptor α loci with a produced transgenic animal having inactivated endogenous T-cell receptor ß loci;

selecting progeny having both inactivated endogenous T-cell receptor α and T-cell receptor ß loci;

inserting transgenes containing active, unrearranged human T-cell receptor loci in an embryo or embryonic stem cell wherein said human T-cell receptor loci are human T-cell receptor α or T-cell receptor ß loci, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene;

crossing a produced transgenic animal having active human T-cell receptor α transgenes with produced transgenic animal having active human T-cell receptor ß-transgenes;

selecting progeny having both active human T-cell receptor α and T-cell receptor ß transgenes wherein the animal is capable of producing T-cells that express human T-cell receptors;

crossing a produced transgenic animal having both inactivated endogenous T-cell receptor α and T-cell receptor ß loci with a produced transgenic animal having both active human T-cell receptor α and T-cell receptor ß transgenes;

selecting progeny having inactivated endogenous T-cell receptor α and T-cell receptor ß loci and containing active human T-cell receptor α and T-cell receptor ß-transgenes; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

42. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by a functional limitation of the loci.

43. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting J segment genes from said loci.

44. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting D segment genes from said loci.

45. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting C segment genes from said loci.

46. (Cancelled)

47. (Previously Presented) The method as in one of claims 38, 39, 41 wherein said transgenes containing the active human T-cell receptor loci comprise, in operable linkage, a plurality of human T-cell receptor V genes, and D and/or J and C genes.

48 – 111. (Cancelled)

112. (Currently amended) A non-human transgenic animal comprising inactivated endogenous T-cell receptor gene loci, said transgenic animal further containing in its genome transgenes composed of unrearranged human T-cell receptor α and β loci, comprising, in operable linkage, a plurality of human T-cell receptor V genes, and their D and /or J and C genes, wherein said animal is capable of productive rearrangement of the human T-cell receptor alpha and beta loci.

113. (Currently amended) A non-human transgenic animal having a germline genome with:

a human T-cell receptor ß chain transgene comprising in operable linkage a plurality of human V genes, and either one or both of the C ß loci and wherein in lymphocytes of said non-human transgenic animal the human T-cell receptor ß chain transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human ß chain in detectable amounts in response to antigenic stimulation;

a human T-cell receptor α chain transgene with plurality of human V gene segments, human J gene segments, the human C α coding exon, and a human 3' downstream α-enhancer; and wherein in lymphocytes of said non-human transgenic animal the human T-cell receptor α chain transgene undergoes productive VJ~~VDJ~~ rearrangement and produces T-cells expressing

TCR human α-chain in detectable amounts in response to antigenic stimulation;

an endogenous TCR ß chain loci having an inactivated ß chain gene; and

an endogenous TCR α chain loci having an inactivated α chain gene.